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EFFICACY OF SKIN PIGMENT EXTRACT OF MARINE CEPHALOPOD, *UROTEUTHIS SIBOGAE* ON THE HAEMATOLOGICAL PARAMETERS IN SPRAGUE DAWLEY RATS INDUCED WITH BREAST CANCER

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ABSTRACT

Comprehensive *in-vivo* experiments were conducted using breast cancer-induced animal models to evaluate the therapeutic effects of the Indian squid, *Uroteuthis sibogae* skin pigment extract and focusing on its efficacy against breast cancer. Anti-neoplastic effect against DMBA induced breast carcinogenesis was elucidated in female Sprague-Dawley rats. Body weight significantly declined in the rats that received the carcinogen, while a reverse trend in the group of rats treated with the skin pigment extract and commercial doxorubicin drug was observed. Tumor characteristics were visible in the all groups of rats with different treatment regime other than the control rats. Haematological parameters show total RBC and the platelet count decline in group- II DMBA induced and group - IV doxorubicin treated animals. The total number of WBC was found to be significantly increased in group- II breast tumor induced and group- IV doxorubicin treated animals when compared with their respective control group of animals. The hemoglobin content and hematocrit were significantly decreased in DMBA induced and doxorubicin treated animals when compared to control group. Red blood cell indices were significantly

decreased in group-II animals treated with DMBA when compared with control group. Administration of skin pigment extracts to breast cancer-induced group-III animals resulted in the restoration of RBC, WBC, and hemoglobin levels towards normal.

KEYWORDS: *Uroteuthis sibogae,* DMBA, Skin pigment extract, Sprague-Dawley rats, Haematology.

1. INTRODUCTION

The skin of the Indian squid, *Uroteuthis sibogae* are mostly considered as a discard from the animal, but the squid skin has significant bioactive compounds. Among the compounds responsible for the pigmentation in the cephalopods are ommochromes, which are mainly synthesized in the skin of marine molluscs. Ommochromes, produce colour in the biological system, preventing peroxidation in cellular liposomes (Sutherland et al., 2008).

Dontsov et al. (2020) reported that naturally occurring pigments possessing biological activity represent promising pharmacological agents for the prevention and management of disorders associated with oxidative stress. According to their findings, natural phenoxazinone compounds, characterized by a tricyclic iminoquinone framework, are integral structural components of ommochromes such as xanthommatin and dihydroxanthommatin, Cephalopods were considered as significant resources of bioactive metabolites with prominent bioactive potentials (Chakraborty and Joy, 2017).

Phenoxazines have gained prominence in medicine as pharmacological lead structures. Phenoxazines are tricyclic heterocycles made up of two benzene rings joined together by an oxazine structure (Katsamakas et al., 2016). The compound's colour and intercalative properties are due to the heterocyclic fragment, a phenoxazine derivative with a quinonimine part and this made the researchers believe that various derivatives of phenoxazine should also possess anticancer properties (Chandrita Sadhu and Amrit Krishna Mitra, 2023). The antiproliferative properties of a number of polycyclic phenoxazine compounds were studied (Prinz et al., 2011). Phenoxazine derivatives, have attracted attention due to a wide range of biological properties, including anti-bacterial, anti-viral, anti-tumor, antioxidant and anti-inflammatory activities (Kozlovskaya et al., 2019; 2021; Shukla et al ., 2021).

Various research studies have strived for several structural modifications targeting phenoxazines and its new derivatives on a number of cell lines, A-431 epidermoid carcinoma

cells, A549 lung cancer cells, breast adenocarcinoma MCF7 cells and MDA-MB-231 cells, HT-1080 epithelial cells derived from the fibrosarcoma connective tissue, T24 urinary bladder transitional carcinoma cells revealed promising results by MTT cell viability assay (Papadopoulou et al., 2026).

Since the bioactivity-driven screening of phenoxazine derivatives focused on putative anti-cancer activities using a number of human cell lines derived from diverse types of cancer, studies on animal models are scarce. This pilot study aims to ascertain the effect of ethanolic extract of natural skin pigments obtained from squid, *Uroteuthis sibogae* on induced breast cancer in Sprague-Dawley rats. The progress, challenges and prospects in medicinal applications of phenoxazine moiety derived ommochrome compounds will provide greater insight into the development of future derivatives with improved properties.

2. MATERIALS AND METHODS

2.1. Preparation of ethanolic extract and lyophilization of skin extracts: Squid samples was washed with distilled water. Dissections were made for removing the skin membrane. The outer skin membrane was gently removed using sterile forceps and washed with distilled water and cut into small pieces. Using 10 ml of ethanol, 10g of the skin tissues were homogenized by using mortar and pestle following aseptic techniques. To the homogenate 100 ml ethanol was added and incubated for 72 hours at room temperature before further processing. The extracted skin homogenate was then lyophilized using phosphate buffered saline in the ratio of 1:10 using a lyophilizer.

2.2. Isolation and concentration of skin pigments: The isolation of the chromatophoric granules and the extraction of the pigments (ommochromes) were carried out by means of two processes of solubilization of the ommochromes in acidified ethanol (1% v/v HCl), followed by successive steps of centrifugation. Pigment extraction was done using acidified ethanol. according to the method of Van den Branden and Decleir, 1976.

The pigment extraction process from the lyophilized skin extract (w/v) in acidified ethanol (99:1; Ethanol:HCl), The mixture was kept under constant stirring for 10 min in a Vortex and sonicated in an ultrasonic bath for 10 min at room temperature 25^{o}C followed by centrifugation at 10,000 × *g* for 15 min. The pigmented supernatant was collected. The extraction was repeated three times.

The supernatant obtained was collected and concentrated under vacuum in a rotary evaporator (Buchi) at 30°C and further evaporated to atmospheric conditions. A rotating evaporator with reduced pressure concentrated the solvents and extract was filtered through Whatman No.1 filter paper. The filtrate was poured in previously weighed petridishes and left for further evaporation to dryness. A dark brownish red sticky viscous residue was produded. The dried extract was used for further experimental analysis.

2.3. Institutional Animal Ethical Committee Approval for the present study: All procedures involving animal testing , experiments, habitat and victuals were designed and strictly performed in accordance with CPCSEA guidelines (Committee for the Purpose of Control and Supervision of Experiments on Animals, Ministry of Social Justice and Empowerment, Government of India, New Delhi). The Institutional Animal Ethical Committee (IAEC) (Approval No; SU / CLATR / IAEC/XXIII/36/2024; dated 29.06.2024) of Sathyabama Institute of Science and Technology, Chennai. India authorized and approved the present experiment. The rats had unrestricted access to food and water. Before the studies started, the rats were allowed to acclimatise for seven days.

2.3.1. Maintenance of animals - Sprague Dawley rat model: All experiments were done with written approval from the Institutes Animal Ethics Committee. All guidelines for maintenance and use of animals were followed. Female SD rats (50–55 days old) were used in this study. The animals were purchased from Biogen, Bangalore. Housed and maintained in Centre for Laboratory Animal Technology and Research, Central Animal House Facility, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India. Careful pre-experimental preparation was done. In order to monitor standard parameters such as temperature of 23°C ± 2°C, humidity of 60–70%, and the standard ratio of artificial light to dark (12 h:12 h) (lights on from 6 am, light intensity 150 lux per cage), the rats used in the experiments were housed in standard polypropylene cages with five rats per cage. The animals were fed on commercially available pelleted diet (M/S Hindustan Foods Ltd, Bangalore, India) and were provided with tap water for drinking during the trial. Every day, the sawdust was replaced and the rat cages were cleaned.

2.3.2. Experimental design: The animals were divided into four groups of six animals each.

Group-I: Animals received 0.5 mL corn oil thrice a week orally for 14 weeks.

Group-II: Eight-week-old female SD rats were given a single oral gastric intubation dose of

25 mg kg^{-1} (7,12-Dimethyl benz(a)anthracene, DMBA) dissolved in 0.5 mL of maize oil to induce mammary cancer. From the day of induction (DMBA alone), the rats were given 14 weeks to acquire a significant mass of mammary carcinoma.

Group-III: Mammary carcinoma was induced as in group-II rats and post- treatment with crude extracts of skin pigments from squid species taken for the study. The extract given was 150 mg kg^{-1} d^{-1} dissolved in 0.5 mL corn oil and given at 8 cycles for 4 weeks at the site close to the tumor area. Treatment started as soon as the tumor size reached 50 mm^3 (DMBA + Skin pigment extract).

Group-IV: Doxorubicin, a commercial drug, was administered subcutaneously to rats in a centyl-methyl-cellulose suspension at a dose of 100 mg/kg every second day starting on the day the tumors reached a volume threshold of 50 mm^3.

2.3. Tumor induction: Female SD rats, weighing (150 ±10 g) were used to induce tumors in the mammary glands. DMBA is an odourless, yellowish green compound that is derived from phenanthrene, a powerful laboratory carcinogen and immunosuppressant. This compound was administered intragastrically as single dosage for Group-II animals, while Group - III animals were used to study the chemotherapeutic potential of crude extracts of skin pigments of squid. Following the administration of DMBA and crude skin pigment extract, both groups were monitored and palpated starting in the eighth week to assess the growth, location, and size of tumours. Every week, the animals were weighed. Over the course of the experiment, the animal's body weight was noted.

2.4. Collection of blood for analysis: After the experimental period, the animals were anesthetized using diethyl ether and sacrificed by cervical decapitation. After euthanizing, blood was collected. The orbital piercing procedure was used to collect the blood. Heparinised microcrit capillary tubes were used to collect 1.0 mL of blood via the orbital sinus using the retro-orbital method. The blood was then transferred to the vacutainer blood collection tube (Kumar *et al*., 2017). The breast tissues were excised immediately. All tissues were washed in 0.9 % NaCl and frozen rapidly at -80°C until further analysis. The mammary tumors were measured and findings were recorded.

2.5. Evaluation of mammary tumor volume and tumor incidence: The volume of breast tumors was determined using a vernier calipers. After achieving a tumor of upto 50 mm^3, animals were sacrificed. The tumor volume was calculated using, V = (W(2) x L)/2, where V is tumor volume, W is tumor width, L is tumor length for caliper measurements. For a

sufficient amount of 100% tumor incidence, the SD rats were subjected to 25 mg kg^{-1} of body weight of DMBA which in turn induced mammary tumors in 8-14 weeks. Tumor incidence is the percentage of tumors present in a group.

2.6. Hematological parameters: Blood samples were collected under anaesthesia at the end of the experimental period. EDTA coated tubes were used for collecting the samples for haematological analysis. The acquired blood samples were analysed for complete blood count. Red blood cell (RBC), white blood cell (WBC) and platelet count, haemoglobin (Hb), hematocrit (HCT), mean cell volume (MCV), mean capsular hemoglobin (MCH) and mean cell hemoglobin concentration (MCHC) were analyzed using a fully automated hematology bidirectional analyzer (6 Part Differential Sysmex XN-1000, Japan).

2.7. Statistical analysis

Data was expressed as Mean ± SD for three replicates. Software package 'Minitab 19' version was used to carry out the statistical analysis by one-way analysis of variance (ANOVA), and tests of statistical significance were determined at the 5% (represent 95% confidence limit) and 1% (represent 99% confidence limit) levels.

3. RESULTS

The anti-cancer potential of *Uroteuthis sibogae* skin pigment extract was evaluated in female Sprague Dawley (SD) rats with DMBA-induced breast cancer. Hematological parameters, were assessed at the conclusion of the experimental period. In this study, DMBA was administered to 50–55-day-old SD rats via oral route, while the skin pigment extract was delivered orally through gavage and doxorubicin by subcutaneous injection.

3.1. Body weight analysis: SD rats exhibited high susceptibility to DMBA-induced stress. Body weights were recorded every 15 days throughout the completion of the study. The initial weights at the start of the experiment and the final weights at the end of the 14-week experimental period were recorded. Rats administered with DMBA alone showed a significant reduction in body weight. Conversely, rats treated with the skin pigment extract or doxorubicin demonstrated a reversal of this weight loss trend. Notably, the increase in body weight was more pronounced in Group III rats receiving the skin pigment extract compared to Group IV rats treated with doxorubicin (Table 1; Fig. 1).

Table 1: Effect of skin pigment extract on body weight in control and experimental animals.

Experimental groups	Initial weight (gm)	Final weight (gm)
Group- I- Control	150.0 ± 3.81[a]	230.0 ± 1.36[a]
Group- II - DMBA induced	147.0 ± 2.74[a]	165.6 ± 1.60[d]
Group- III- DMBA induced and co-treated with skin extract	151.0 ± 2.00[a]	185.2 ± 1.60[b]
Group- IV-Doxorubicin treated	151.0 ± 2.00[a]	176.0 ± 1.36[c]

Values are Mean ± SD (n=5) observations; Across the column, values with different alphabetical letters superscripted are significantly different at (P<0.05); same alphabetical letters do not differ significantly.

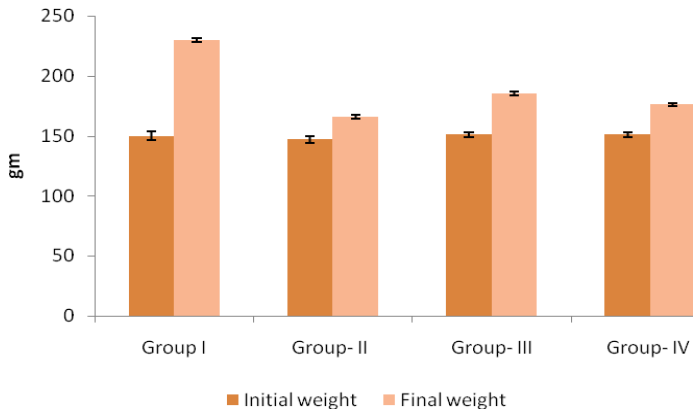

Fig. 1: Graphical representation of body weight in control and experimental animals.

3.2. Gross examination of tumor development: Gross examination of the mammary tissues in both control and experimental groups was conducted monthly throughout the study. The breast tissue of the control rats in Group I appeared normal, with intact surface morphology and no palpable tumors. In contrast, rats in Group II, which were induced with DMBA, developed noticeable tumor masses in the ventral region, specifically around the lower abdominal mammary teats on the right flank. Rats in Group IV, treated with the standard chemotherapeutic agent doxorubicin, displayed reduced tumor formation compared to Group II. Both Group III (skin pigment extract) and Group IV treatments significantly inhibited tumor progression. No mortality was observed in any of the experimental groups during the study period.

3.3. Tumor characteristics and incidence of tumor: The excised mammary tissues were analyzed to assess tumor weight, volume, and incidence across control and experimental groups. Control rats, which received only corn oil, showed no anatomical or pathological

alterations in the mammary gland. In contrast, tumor development was evident in the three DMBA-treated groups, displaying varying degrees of progression depending on the treatment. In the DMBA-treated group (Group II), the average tumor weight reached approximately 17.64 g, tumor volume was 810.56 mm^3, and tumor incidence was 9.46 % among the remaining animals at the end of the experimental period. Co-treatment with the skin pigment extract (Group III) significantly reduced tumor burden, with tumor weight decreasing to 9.46 g, tumor volume to 442.39 mm^3, and tumor incidence to 3.65% in the five rats. Rats treated with doxorubicin exhibited similar trends, albeit to a slightly lesser extent. Tumor induction occurred with nearly 100% incidence within 14 weeks in DMBA treated animals only. Notably, in Group III, both the size and number of tumors were markedly lower, with an absence of well-differentiated carcinomas compared to Group II (Table 2; Fig. 2).

Table 2: Effect of skin pigment extract on tumor characteristics in control and experimental animals.

Experimental groups	Tumor weight (gm)	Tumor incidence (%)	Tumor volume (mm^3)
Group-I- Control	-	-	-
Group-II- DMBA induced	17.64 ± 2.76^a	9.46 ± 1.5^a	810.56 ± 205.38^a
Group-III -DMBA induced and co-treated with skin extract	9.46 ± 1.00^b	3.66 ± 0.57^b	442.39 ± 183.08^b
Group-IV- Doxorubicin treated	7.83 ± 0.74^c	2.33 ± 0.57^c	181.42 ± 36.97^c

Values are Mean ± SD (n=5) observations; Across the rows, values with different alphabetical letters superscripted are significantly different at ($P<0.05$); same alphabetical letters do not differ significantly.

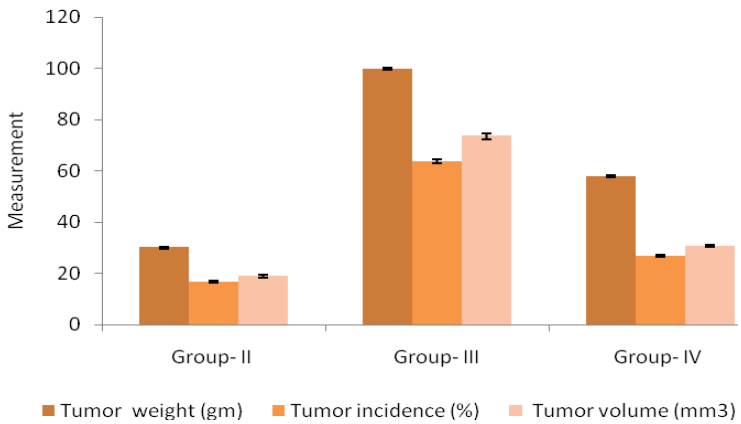

Fig. 2: Representation of tumor characteristics in control and experimental animals.

3.4. Blood cell analysis: Hematological analysis revealed a significant decline in total red blood cell and platelet counts in the DMBA-induced group (Group II) and the doxorubicin-treated group (Group IV) compared to the control animals (Group I). In contrast, rats co-treated with the skin pigment extract (Group III) exhibited a significant recovery in RBC and platelet levels relative to the DMBA-only group. WBC total count were markedly elevated in Group II and Group IV animals compared to controls, indicating an inflammatory or immune response associated with tumor progression or chemotherapeutic stress. Conversely, Group III animals, which received both DMBA and skin pigment extract, demonstrated a reduction in WBC counts, suggesting a modulatory effect of the extract on systemic immune response (Table 3; Fig. 3).

Table 3: Effect of skin pigment extract on blood cells in control and experimental animals.

Experimental groups	RBC ($\times10^6$/µL)	WBC ($\times10^3$/µL)	Platelets ($\times10^5$/µL)	p- value
Group- I- Control	8.00 ± 0.06^a	7.20 ± 0.06^d	8.40 ± 0.06^a	< 0.001
Group- II - DMBA induced	6.20 ± 0.06^c	11.50 ± 0.17^a	6.20 ± 0.06^c	
Group- III- DMBA induced and co-treated with skin extract	7.10 ± 0.06^b	8.40 ± 0.06^c	7.90 ± 0.06^b	
Group- IV- Doxorubicin treated	5.20 ± 0.06^d	9.77 ± 0.15^b	5.40 ± 0.06^d	

Values are Mean ± SD (n=3) observations; Across the columns, values with different alphabetical letters superscripted are significantly different at (P<0.05); same alphabetical letters do not differ significantly.

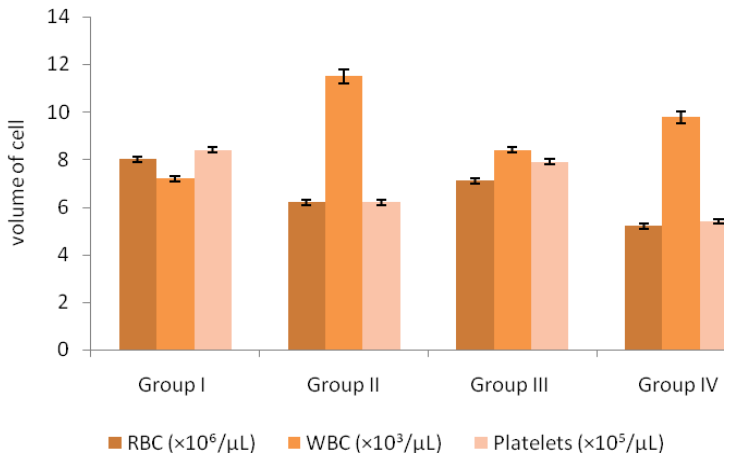

Fig. 3: Graphical representation of blood cells in control and experimental animals.

3.5. Analysis of hemoglobin content, hematocrit levels and red cell indices: Hb content and HCT levels were significantly reduced in DMBA-induced rats (Group II) and doxorubicin-treated rats (Group IV) compared to the control group (Group I). In contrast, rats treated with the skin pigment extract (Group III) exhibited a marked increase in both hemoglobin and hematocrit levels relative to Groups II and IV, indicating a protective effect of the extract on erythropoiesis (Table 4; Fig. 4).

Table 4: Effect of skin pigment extract on Hb and HCT in control and experimental animals.

Experimental groups	Hb (g/dL)	Haematocrit (%)	p -value
Group- I- Control	15.00± 0.06[a]	43.03 ± 0.09[a]	< 0.0001
Group- II - DMBA induced	11.17± 0.09[c]	33.10 ± 0.12[c]	
Group- III- DMBA induced and co-treated with skin extract	13.40± 0.06[b]	39.37 ± 0.15[b]	
Group- IV-Doxorubicin treated	10.10 ± 0.06[d]	30.47 ± 0.15[d]	

Values are Mean ± SD (n=3) observations; Across the columns, values with different alphabetical letters superscripted are significantly different at (P<0.05); same alphabetical letters do not differ significantly.

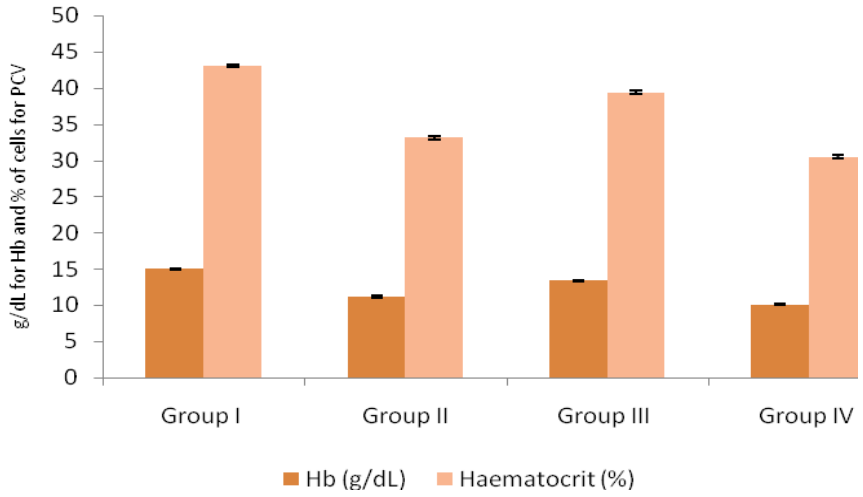

Fig. 4: Graphical representation of Hb and HCT in control and experimental animals.

Analysis of red blood cell indices showed that MCV, MCH, and MCHC were significantly lower in Group II compared to controls. Treatment with the skin pigment extract (Group III) restored these indices, with values significantly higher than those observed in the DMBA-induced group. No significant differences in MCH and MCHC were found between the

control group and the extract-treated group. In Group IV (doxorubicin-treated), MCV and MCH increased, while MCHC decreased relative to the other groups, reflecting differential effects of the chemotherapeutic agent on red blood cell morphology (Table 5; Fig.5).

Table 5: Effect of skin pigment extract on red cell indices in control and experimental animals.

Experimental groups	MCV (fL)	MCH (pg)	MCHC (g/dL)	p- value
Group- I- Control	53.67 ± 0.33^{b}	18.80 ± 0.06^{b}	34.77 ± 0.09^{b}	<0.0001
Group- II - DMBA induced	52.00 ± 0.58^{c}	17.80 ± 0.06^{c}	33.80 ± 0.06^{c}	
Group- III- DMBA induced and co-treated with skin extract	55.00 ± 0.58^{a}	18.50 ± 0.06^{b}	34.23 ± 0.09^{b}	
Group- IV-Doxorubicin treated	57.67 ± 0.33^{a}	19.10 ± 0.06^{a}	32.90 ± 0.09^{c}	

Values are Mean ± SD (n=3) observations; Across the columns, values with different alphabetical letters superscripted are significantly different at (P<0.05); same alphabetical letters do not differ significantly.

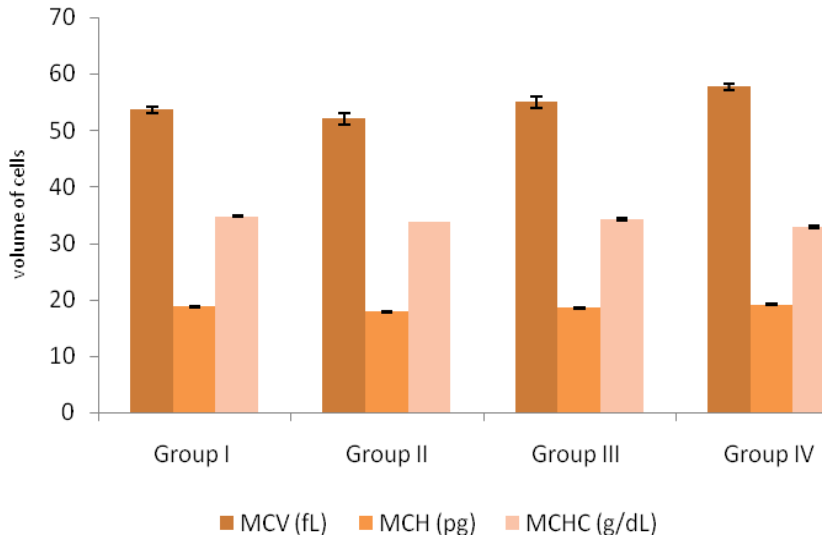

Fig. 5: Graphical representation of red cell indices in control and experimental animals.

4. DISCUSSION

Chemotherapy remains a key adjuvant therapy for both early-stage and metastatic breast cancer (Moo et al., 2018). However, its clinical application is often limited by severe adverse effects, including weight loss, myocardial injury, bone marrow suppression, compromised

immune function, and osteoporosis.

Doxorubicin, is a widely used chemotherapeutic agent for the treatment of human breast cancer (Fan et al., 2017). Despite its efficacy, the commercial drug is associated with significant side effects, such as cardiotoxicity, myelosuppression, immunodeficiency and bone density loss (Zhou et al., 2020). These limitations underscore the need for safer and more effective therapeutic alternatives.

In this context, natural bioactive compounds have attracted considerable attention due to their potential to reduce the toxicity and side effects associated with conventional chemotherapy (Waks and Winer, 2019). The present study investigates the anticancer potential of the ethanolic skin pigment extract of the Indian squid, *Uroteuthis sibogae*, focusing on its efficacy against breast cancer.

In the present study, animals treated with the skin pigment extract of *Uroteuthis sibogae* exhibited a significant attenuation of weight loss compared to the untreated control group. Weight loss is often one of the earliest and most evident indicators of cancer progression and is closely linked to disease severity. In both clinical and preclinical models, this loss is primarily attributed to muscle wasting, which can exacerbate morbidity and increase mortality rates (Gul et al., 2023). This effect is likely attributed to the bioactive ommochrome constituents of the extract, which may exert antitumor activity while preserving overall body mass. The observed increase in body weight in the pigment extract-treated groups aligns with previous findings demonstrating the protective effects of bioactive compounds in preventing cancer (Kehinde et al., 2020).

Tumor incidence, growth, weight, metastasis, and latency are critical parameters for assessing disease progression and therapeutic efficacy. In the present study, evaluation of tumor volume and related characteristics revealed that animals treated with the skin pigment extract of *Uroteuthis sibogae* exhibited a marked reduction in tumor size, weight, and other pathological features compared to cancer induced untreated controls. These findings confirm the anti-proliferative and antitumor potential of the extract. Similar outcomes have been reported in previous studies where combined treatments with bioactive compounds, such as ω-3 polyunsaturated fatty acids, along with conventional antitumor agents, resulted in significant reductions in tumor metastasis and progression (Guo et al., 2021). The results of the present study demonstrate that skin pigment extract effectively reduced tumor volume and

overall tumor burden.

Complete blood count analysis provides insights into the cellular immune response in cancer-bearing individuals (Rana et al., 2015). In the present study, DMBA-exposed animals exhibited a significant reduction in RBC count and hemoglobin levels, a common manifestation observed in malignancies (Gaspar et al., 2015). Such hematological deficiencies contribute to anemia, which can exacerbate tumor progression, increase invasiveness, and promote metastasis (Anandakumar et al., 2012). The observed anemia may result from inhibition of globin synthesis, suppression of erythropoiesis, or reduced folic acid levels (Kehinde et al., 2020). Notably, treatment with the skin pigment extract significantly ameliorated alterations in red cell indices, including mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration, suggesting that the bioactive constituents of the extract may alleviate anemia and haemopoiesis during mammary gland carcinogenesis (Jie Ping Zhong et al ., 2009).

Platelets play a crucial role in both inflammation and angiogenesis, as they can be activated by cancer cells to release cytokines, chemokines, and angiogenic mediators that promote tumor progression (Johnson et al., 2016). In the present study, it is suggested that treatment with skin pigment extract mitigated the increase in platelet number and activity, likely through its anti-inflammatory properties. Previous research has reported that activated platelets can protect cancer cells from immune surveillance and facilitate metastasis by generating fibrin networks that enhance tumor cell adhesion to the endothelium (Ghandehari et al., 2018).

Administration of skin pigment extracts to breast cancer-induced rats resulted in the restoration of RBC, WBC, and hemoglobin levels toward normal values. These findings indicate that the skin pigment extract not only exerts anticancer effects but also ameliorates hematological abnormalities commonly associated with breast cancer, supporting its potential therapeutic application.

5. CONCLUSION

The results of the study encompass the idea that cephalopods ought to be a source that could be considered in the discovery of new substances for drug development to ameliorate breast cancer. Moreover, elucidation of the molecular framework of skin pigments constituents may provide a foundation for the development of novel drugs or derivatives. Collectively, this

study establishes a basis for future research aimed at exploring the therapeutic applications of cephalopod-derived ommochromes, particularly in cancer therapy.

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